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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,879	03/31/1999	SUBROTO CHATTERJEE	46906-2-DIV	9227

7590 04/09/2002

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/282,879	CHATTERJEE, SUBROTO	
	Examiner	Art Unit	
	Manjunath N Rao	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 1-15-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/282,879 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 13-17 are now currently pending in this application.

Drawings

This application has been filed with drawings that have been accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 15-17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13, 15-17 are rejected because of the recitation of the phrase "or derivative thereof". While Examiner acknowledges that the specification defines fragments or derivatives as proteins or polypeptides which retain the biological activity of sphingomyelinase (SM), the specification does not define what the metes and bounds of the term "derivative" are. That is to say, whether the derivative is <u>any</u> protein from any source with the same activity or must the protein have some amount of structural homology to SEQ ID NO:2? And if so how much homology must be present to be a derivative? Therefore, the claim as written does not convey the scope of "derivatives" encompassed rendering the claim unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sphingomyelinase (SM) enzyme with SEQ ID NO:2 or fragments of SEQ ID NO:2 possessing the sphingomyelinase activity, does not reasonably provide enablement for any derivatives thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 13 and 15-17 are so broad as to encompass any SM, i.e., any recombinant, mutant, variant, fusion protein etc. from any source which maintains at least 50%, 75% or 95% SM activity as that of SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of SMs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of a single SM.

While recombinant mutagenesis and derivatization techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, or multiple derivatives as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all types of derivatives because the specification does not establish: (A) whether the derivative is any protein from any source with the same activity or whether it is strictly derived from SEQ ID NO:2 and if so regions of the protein structure which may be modified without effecting SM activity; (B) whether the protein must have some amount of structural homology to SEQ ID NO:2, and if so how much homology must be present to be a derivative? and the general tolerance of SM to modification and extent of such tolerance; (C) a rational and predictable scheme for derivatizing SM residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including derivatives of SM. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA

1970)). Without sufficient guidance, determination of derivatives of SM having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17 are directed to polypeptide derivatives corresponding to the sequence of SEQ ID NO:2. Claims 13 and 15-17 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of derived polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art

cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ogita et al. (WO 9518119, 7-6-1995) and Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6). Claims 13-17 in this instant application are drawn to a method of identifying a compound which when used in a reaction comprising sphingomyelin as the substrate, the neutral sphingomyelinase as the enzyme and ceramide as the cleaved product, leads to reduced concentration of the cleavage product such that the identified compound could be used in the diagnosis or treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page

12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes, leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, this reference also does not teach the use of recombinant SM.

Ausubel et al. in their voluminuous manual teach all the techniques related to cloning a known protein starting from its purification stage up to obtaining its cDNA and the recombinant form of the protein. Examiner draws the attention of the applicant to the enclosed pages 10.0.3-10.0.6 wherein the reference teaches how one can obtain the oligonucleotide probe from a purified protein. Other chapters in the book also teach how one skilled in the art can make a

specific cDNA library and use the oligonucleotide probe to clone the specific protein and obtain it in the recombinant form.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with Ogita et al. such that compounds could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this because, when the transmission of signals introduced by IL-1beta and TNF-alpha is blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and a robust and time tested assay method and Ogita et al. provide an assay and demonstrate the existence of a chemical compound which inhibits sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicant has traversed the above rejection of claims 13-17 by amending claim 13 to recite "recombinant human neutral sphingomyelinase" and "amino acid SEQ ID NO:2" and also arguing that the cited references do not provide for any method in which a recombinant SM is used and that the Office's cited combination of references is not the claimed invention and that there is no *prima facie* case of obviousness and the rejection should be withdrawn. Examiner respectfully disagrees. Contrary to applicant's argument Examiner reiterates that the combination of the references does render the above invention *prima facie* obvious as explained in the previous paragraphs. Furthermore, a search of the amino acid sequence databases against the amino acid sequence SEQ ID NO:2 reveals that it matches 100% with the amino acid sequence derived from the same enzyme that was purified by Chatterjee et al. (see enclosed amino acid sequence alignments that has been provided as an evidentiary reference). Applicant's above argument and amendment is still not persuasive to overcome the rejection because even though both the above references do not teach recombinant sphingomyelinase, the reference of Chatterjee et al. does teach the purified enzyme. Applicant has not shown that the recombinant enzyme differs in any material respect from the enzyme purified by Chatterjee et al. Therefore, it would have been obvious to one of ordinary skill in the art to obtain the amino acid sequence of the purified enzyme and clone the gene encoding the above enzyme and make recombinant form of the enzyme for use in such assays.

Applicant also argues that the position taken by the Office is clearly at odds with decisions of Federal Circuit, (referring to the decisions handed down in *In re Deuel* and *In re Bell*) and current USPTO examination practice. Examiner respectfully disagrees with such an argument. Applicant quotes *In re Deuel* and *In re Bell* and argue that disclosure of a protein

sequence does not necessarily render particular DNA molecules encoding the protein obvious and that Office has not reached the threshold addressed by *Deuel* and that the Office has not even cited any protein sequence of the human neutral SM in formulating the rejection. In response, Examiner again retiterates that there is no need for the Office to provide a protein sequence of the human neutral SM in formulating the rejection because of the obviousness to one skilled in the art to obtain the sequence if needed. Applicant's argument taking support from *Deuel* or *Bell* is highly misplaced and is completely without merit. This is because applicant is not claiming DNA or a method based on DNA sequence. While Examiner agrees that disclosure of a purified protein does not necessarily render particular DNA molecules encoding the protein obvious, Examiner would like to point out that applicant's claims are directed to a method of using a recombinant polypeptide and thus cannot apply the decision of *In re Deuel* or *Bell*. Therefore, contrary to the tangential arguments of the applicant the instant obviousness rejection does not fail.

Applicant also argues that Office has relied on knowledge of general gene cloning methods and is not sufficient to render a particular DNA molecule obvious. Here again, applicant's argument is tangential to the subject matter of the claims. Examiner would again like to point out that applicant's claims are drawn to a method of using a polypeptide and not drawn to DNA. Applicant's repeated reference to *In re Bell* is again highly misplaced. In response to the applicant's argument that the Office has relied on general knowledge, Examiner has now included the reference of Ausubel et al. which specifically teaches methods and techniques for obtaining recombinant clones for any protein.

Contrary to applicant's argument, that a worker in possession of applicant's specification only would have readily appreciated the significant advantage of working with recombinant human enzyme, a worker in possession of the above three references provided by the Examiner would readily appreciate the significant advantages of using recombinant human enzyme. The reasons which are stated in Chatterjee et al. reference, that, purifying the enzyme involves manipulating large amounts of human urine and the inconvinience and hazards of working with large amounts of urine samples, would simply motivate one skilled in the art to use the techniques provided in the refernce of Ausubel et al. to obtain the recombinant form of the enzyme using the purified enzyme of Chatterjee et al. Again contrary to applicant's argument, with the availability of a recombinant form of the enzyme it would not be difficult at all to one of ordinary skill in the art to obtain fragments and derivatives of the proteins for performing the above assay.

Applicant also argues that Ogita et al. reference discloses sphingomyelinase inhibitors and not inhibitors of neutral sphingomyelinase of the instant application. Examiner respectfully disagrees with such an argument. While the reference of Ogita et al. does not explicitly state that the assays are for neutral sphingomyelinase, the assay reaction has been performed at pH 7.5 which is very close to the neutral pH which would suggest to one of ordinary skill in the art that the enzyme used by Ogita et al. is neutral sphingomyelinase. Furthermore, there is no disclosure anywhere in the reference that the inhibitors do not act on neutral sphingomyelinase.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao. Ph.D.
4/8/02